PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Philip E. Thorpe, Sophia Ran and Rolf A. Brekken (As Amended)	§	Group Art Unit: 1619
Serial No.: 09/351,149	§	Examiner: Sharareh, S.
Filed: July 12, 1999	§	Atty. Dkt.: 3999.002383
For: CANCER TREATMENT KITS COMPRISING THERAPEUTIC CONJUGATES THAT BIND TO AMINOPHOSPHOLIPIDS	§	

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

Nov. 27, 2001
Date

Shelley P.M. Fussey

DECLARATION OF PHILIP E. THORPE, SOPHIA RAN AND ROLF A. BREKKEN UNDER 37 C.F.R. § 1.131

Assistant Commissioner for Patents
Washington, D.C. 20231

WE, PHILIP E. THORPE, SOPHIA RAN AND ROLF A. BREKKEN, HEREBY DECLARE AS FOLLOWS:

1. We are co-inventors of the subject matter disclosed and claimed in the captioned patent application.

2. I, Philip E. Thorpe, am Professor of Pharmacology and hold the Serena S. Simmons Distinguished Chair in Immunopharmacology at the Simmons Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. I am a British subject and a

permanent resident in the United States. I live at 5311 Nakoma Drive, Dallas, Texas, 75209, U.S.A.

3. I, Sophia Ran, am an Assistant Professor at the Simmons Cancer Center, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. I am a citizen of Israel and a permanent resident in the United States. I live at 5840 Spring Valley Road, #1612, Dallas, Texas, 75240, U.S.A.

4. I, Rolf A. Brekken, am a Postdoctoral Fellow at The Hope Heart Institute, Seattle, Washington. I am a U.S. citizen and live at 14304 25th Ave NE, Seattle, Washington, 98125, U.S.A. Immediately prior to my present employment, I worked in the laboratory of Philip E. Thorpe at The University of Texas Southwestern Medical Center at Dallas ("UT Southwestern").

5. We have reviewed the Official Action dated March 13, 2001 issued by the U.S. Patent and Trademark Office (P.T.O.) charged with assessing the patentability of the captioned patent application. We have also reviewed the references cited in the Official Action: U.S. Patent No. 6,197,278 to Blankenberg, Huang *et al.*, *Science*, 275:547-550, 1997; WO 98/29453; and Fishman *et al.*, *Intl. J. Oncol.*, 10:901-904, 1997.

6. We understand that the P.T.O. has taken the position that the claims examined in the captioned patent application would be obvious to one of skill in this field of study in light of U.S. Patent No. 6,197,278 in view of Huang *et al.*, 1997, WO 98/29453 and Fishman *et al.*, 1997.

7. We disagree with the assessment that the foregoing combination of documents would render the presently claimed subject matter obvious to a scientist working in this field of research.

8. According to the cover page of the document itself, we understand that WO 98/29453 was published on July 09, 1998.

9. We are providing the present declaration and attached documentary evidence to demonstrate that the invention claimed in the captioned patent application was made in the United States prior to July 09, 1998, *i.e.*, prior to the publication date of the WO 98/29453 document.

10. Evidence of the fact that the invention claimed in the captioned patent application was made in the United States prior to July 09, 1998 is shown in the attached Exhibits and described in the following paragraphs. The studies described in the following paragraphs were conducted in Dallas, Texas, in the United States.

11. The captioned patent application claims kits that comprise at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid that is expressed on tumor blood vessels, operatively attached to at least a first therapeutic agent. In these kits, the targeting agent-therapeutic agent constructs are

combined with either a targeting agent-detectable agent construct that also comprises a targeting agent that binds to an aminophospholipid, or with an anti-cancer agent.

12. The claimed targeting agent-therapeutic agent constructs include targeting agents that bind to the aminophospholipid, phosphatidylserine (PS); and targeting agents that bind to the aminophospholipid, phosphatidylethanolamine (PE). The targeting agents may be anti-aminophospholipid antibodies, such as anti-PS or anti-PE antibodies; or aminophospholipid binding proteins, such as annexins, *e.g.*, annexin V, or a kininogen.

13. Exemplary evidence of the concept of certain aspects of the claimed invention is provided in **Exhibit A**, a copy of correspondence dated prior to July 09, 1998 from Philip E. Thorpe and Rolf A. Brekken to Shelley P.M. Fussey, then employed at the law firm of Arnold, White & Durkee. The correspondence describes those aspects of the invention for targeting therapeutic agents, such as drugs or coagulants, to tumor blood vessels for tumor therapy or imaging using annexins, such as annexin V, which bind to phosphatidylserine.

14. The correspondence of **Exhibit A**, dated prior to July 09, 1998, describes the rationale for using annexins to home selectively to tumor vascular endothelium after systemic administration. This correspondence describes making chemical constructs between annexins and drugs or coagulants, as well as fusing genes encoding annexins and cytotoxic proteins (*e.g.*, diphtheria toxin or ricin) or coagulants (*e.g.*, tissue factor, factor Xa, thrombin). It is also explained that radionuclides or imaging agents can be attached to annexins to produce reagents for imaging tumor vasculature.

15. Evidence of the generation of a targeting agent-therapeutic agent construct in which the targeting agent is annexin V and the therapeutic agent is the coagulant truncated tissue factor (tTF) is shown in **Exhibit B**, copies of laboratory notebook pages dated prior to July 09, 1998. The data of **Exhibit B** shows results from construction and fractionation techniques, culminating in samples of purified annexin V-tTF shown on reducing and non-reducing gels.

16. The use of an annexin V-tTF targeting agent-therapeutic agent construct to successfully treat tumors *in vivo* is shown in **Exhibit C**, which represents the data from studies conducted prior to July 09, 1998.

17. In the studies depicted in **Exhibit C**, an annexin V-tTF conjugate was administered to nu/nu mice with solid tumors. The tumors were formed from human HT29 colorectal carcinoma cells that gave rise to tumors of at least about 1.2 cm^3. The annexin V-tTF construct was administered intravenously and allowed to circulate for 24 hours. Saline-treated mice were separately maintained as control animals. After the one day treatment period, the mice were sacrificed and exsanguinated and the tumors and major organs were harvested for analysis.

18. **Exhibit C**, based on studies conducted prior to July 09, 1998, shows that the annexin V-tTF conjugate induced specific tumor blood vessel coagulation in HT29 tumor bearing mice. Approximately 55% of the tumor blood vessels in the annexin V-tTF conjugate treated animals were thrombosed following a single injection. In contrast, only 12% of the tumor vasculature in the control animals showed evidence of thrombosis.

19. Exemplary evidence of the concept of those aspects of the claimed invention in which the targeting agent of the targeting agent-therapeutic agent construct is an antibody is shown in **Exhibit D**, a copy of correspondence dated prior to July 09, 1998 from Philip E. Thorpe to Dr. Neal S. Rote of Wright State University. This correspondence requests samples of anti-PS antibodies from Dr. Rote, so that Drs. Thorpe and Ran can proceed with a fuller study after the inventors' finding that phosphatidylserine is a marker of tumor vascular endothelium. The anti-cardiolipin antibodies requested are for use as a control in the planned studies.

20. The correspondence of **Exhibit D**, dated prior to July 09, 1998, describes the preparation and testing of targeting agent-therapeutic agent constructs in the form of anti-PS antibodies linked to tissue factor. These are described as anti-PS-tissue factor "coaguligands". We employ the term "coaguligand" to refer to a targeting agent-therapeutic agent construct in which a targeting agent that binds to a marker of tumor vasculature is linked to a coagulant. Thus, an "anti-PS-tissue factor coaguligand", as described in this correspondence, is an antibody directed against phosphatidylserine linked to a coagulant based on the tissue factor molecule. The correspondence explains that antibody (IgM) purification and conjugation will be performed by Drs. Thorpe and Ran.

21. Evidence of the shipment of antibodies against phosphatidylserine from Dr. Neal Rote to Drs. Thorpe and Ran at a date prior to July 09, 1998 is shown in the correspondence from Dr. Thorpe to Mr. Richard U. Rodriguez, of the Office of Legal Affairs and Technology Transfer at UT Southwestern, also dated prior to July 09 (**Exhibit E**).

22. Additional evidence concerning the existence of this invention prior to July 09, 1998 is shown in **Exhibit F**, a copy of correspondence from Mr. Louis T. Pirkey of the law firm of Arnold, White & Durkee to Mr. Ray Wheatley of the Office of Legal Affairs & Technology Transfer at UT Southwestern. This correspondence, dated prior to July 09, 1998, formally acknowledges receipt of an invention disclosure entitled "Cancer Treatment Using Antibody Conjugates to Phosphatidylserine" and lists the inventors as "Thorpe and Ran". The correspondence includes the particular file code "UTSD:556", which still forms the basis of UT Southwestern's file reference for the captioned application (UTSD:556--2), and confirms Mr. Wheatley's request that the matter be handled by Shelley Fussey, then employed at the law firm of Arnold, White & Durkee.

23. **Exhibit G** is a copy of additional correspondence dated prior to July 09, 1998 from Mr. Wheatley of UT Southwestern to Shelley Fussey. The correspondence refers to "our phone conference today with Dr. Thorpe", *i.e.*, a telephone conference held prior to July 09, 1998, and authorizes the filing of two provisional patent applications. The correspondence of **Exhibit G** particularly itemizes the inclusion of "coaguligand" effector molecules and "other" effector molecules, which were included in the claims of the provisional application that was filed (see below).

24. We, Philip E. Thorpe and Sophia Ran, recall that a lengthy and detailed draft of the provisional application was prepared by Shelley Fussey and forwarded for our review prior to July 09, 1998. I, Philip E. Thorpe, particularly recall meeting with Shelley Fussey, who traveled

to Dallas to discuss the near-to-final draft of the application prior to July 09, 1998, and I have recorded this meeting on my calendar for the date in question.

25. From the time of our documented development of the invention prior to July 09, 1998, we worked diligently on various aspects of the invention in the United States up to and including July 13, 1998, when the first U.S. provisional patent application directed to our invention was filed.

26. **Exhibit H** shows front page, claims and abstract of the first U.S. provisional patent application directed to our invention that was filed on July 13, 1998. The claims include targeting agents that bind to phosphatidylserine, as represented at least in claims 3, 6, 9, 12, 15, 18, 123, 131 and 145; claims in which the targeting agent is an anti-aminophospholipid antibody or antigen-binding fragment thereof, as represented at least in claims 19-41, 48, 75, 126, 132, 133, 143-147, 151 and 153; and claims in which the targeting agent is an aminophospholipid binding protein or an aminophospholipid-binding fragment thereof, as represented at least in claims 42-46 and 127-128, 134-136, 148, 149 and 152. As outlined in the correspondence of **Exhibit G**, the claims in this provisional application include "coaguligands", as represented at least in claims 59-67, 138, 139, 146 and 147, and "other" effector molecules, as represented at least in claims 51-58 and 137 (**Exhibit H**). Kits comprising the range of targeting agent-therapeutic agent constructs are particularly represented by claims 155-159.

27. From a time prior to July 09, 1998, through July 13, 1998 to the present time, we have continued to work diligently on various aspects of the claimed invention in the United States.

28. We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

11/16/01
Date

Philip E. Thorpe

11/16/01
Date

Sophia Ran

Sophia Ran

Date

Rolf A. Brekken

27. From a time prior to July 09, 1998, through July 13, 1998 to the present time, we have continued to work diligently on various aspects of the claimed invention in the United States.

28. We hereby declare that all statements made herein of our knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date	Philip E. Thorpe
Date	Sophia Ran
9/13/01 Date	Rolf A. Brekken